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(54) Title: INTERFERON-ALPHA INDUCED GENES

(57) Abstract: The present disclosure relates to identification of genes upregulated by interferon-α administration, in particular the human genes corresponding to the cDNA sequences in GenBank designated g4586459, g2342476, g3327161 and g4529886. Determination of expression products of these genes is proposed as having utility in predicting responsiveness to treatment with interferon-α and other interferons which act at the Type I interferon receptor. Therapeutic use of the proteins encoded by the same genes is also envisaged.

INTERFERON-ALPHA INDUCED GENES

Field of the Invention

The present invention relates to identification of genes upregulated by interferon-α (IFN-α) administration. Detection of expression products of these genes may thus find use in predicting responsiveness to IFN-α and other interferons which act at the Type 1 interferon receptor. Therapeutic use of the proteins encoded by the same genes is also envisaged.

Background of the Invention

IFN-α is widely used for the treatment of a number of disorders. Disorders which may be treated using IFN-α include neoplastic diseases such as leukemia, lymphomas, and solid tumours, AIDS-related Kaposi's sarcoma and viral infections such as chronic hepatitis. IFN-α has also been proposed for administration via the oromucosal route for the treatment of autoimmune, mycobacterial, neurodegenerative, parasitic and viral disease. In particular, IFN-α has been proposed, for example, for the treatment of multiple sclerosis, leprosy, tuberculosis, encephalitis, malaria, cervical cancer, genital herpes, hepatitis B and C, HIV, HPV and HSV-1 and 2. It has also been suggested for the treatment of arthritis, lupus and diabetes. Neoplastic diseases such as multiple myeloma, hairy cell leukemia, chronic myelogenous leukemia, low grade lymphoma, cutaneous T-cell lymphoma, carcinoid tumours, cervical cancer, sarcomas including Kaposi's sarcoma, kidney tumours, carcinomas including renal cell carcinoma, hepatic cellular carcinoma, nasopharyngeal carcinoma, haematological malignancies, colorectal cancer, glioblastoma, laryngeal papillomas, lung cancer, colon cancer, malignant melanoma and brain tumours are also suggested as being treatable by administration of IFN-via the oromucosal route, i.e. the oral route or the nasal route.

IFN-α is a member of the Type 1 interferon family, which exert their characteristic biological activities through interaction with the Type 1 interferon receptor. Other Type 1 interferons include IFN-β, IFN-ω and IFN-τ.

Unfortunately, not all potential patients for treatment with a Type 1 interferon such as interferon-α, particularly, for example, patients suffering from chronic viral hepatitis, neoplastic disease and relapsing remitting multiple sclerosis, respond favourably to Type 1 interferon therapy and only a fraction of those who do respond exhibit long-term benefit. The inability of the physician to confidently predict the therapeutic outcome of Type 1 interferon treatment raises serious concerns as to the cost-benefit ratio of such treatment, not only in terms of wastage of an expensive biopharmaceutical and lost time in therapy, but also in terms of the serious side effects to which the patient is exposed. Furthermore, abnormal production of IFN-α has been shown to be associated with a number of autoimmune diseases. For these reasons, there is much interest in identifying Type 1 interferon responsive genes since Type 1 interferons exert their therapeutic action by modulating the expression of a number of genes. Indeed, it is the specific pattern of gene expression induced by Type 1 interferon treatment that determines whether a patient will respond favourably or not to the treatment.

Summary of the Invention

It has now been found that the human genes corresponding to the cDNA sequences in GenBank assigned accession nos. g4586459, g2342476, g3327161 and g4529886, correspond to a mouse gene upregulated by administration of IFN-α by an oromucosal route or intravenously. These human genes are thus now also designated an IFN-α upregulated gene.

The proteins corresponding to GenBank cDNAs g4586459, g2342476, g3327161 and g4529886 have previously had no assigned function. These proteins (referred to below as HuIFRG-1, HuIFRG-2, HuIFRG-3 and HuIFRG-4 proteins respectively), and functional variants thereof, are now envisaged as therapeutic

agents, in particular for use as an anti-viral, anti-tumour or immunomodulatory agent. For example, they may be used in the treatment of autoimmune, mycobacterial, neurodegenerative, parasitic or viral disease, arthritis, diabetes, lupus, multiple sclerosis, leprosy, tuberculosis, encephalitis, malaria, cervical cancer, genital herpes, hepatitis B or C, HIV, HPV, HSV-1 or 2, or neoplastic disease such as multiple myeloma, hairy cell leukemia, chronic myelogenous leukemia, low grade lymphoma, cutaneous T-cell lymphoma, carcinoid tumours, cervical cancer, sarcomas including Kaposi's sarcoma, kidney tumours, carcinomas including renal cell carcinoma, hepatic cellular carcinoma, nasopharyngeal carcinoma, haematological malignancies, colorectal cancer, glioblastoma, laryngeal papillomas, lung cancer, colon cancer, malignant melanoma or brain tumours. In other words, such proteins may find use in treating any Type 1 interferon treatable disease.

Determination of the level of HuIFRG-1, HuIFRG-2, HuIFRG-3 or HuIFRG-4 proteins or a naturally-occurring variant thereof, or the corresponding mRNA, in cell samples of Type 1 interferon-treated patients, e.g. patients treated with IFN-α, e.g. such as by the oromucosal route or intravenously, may also be used to predict responsiveness to such treatment. It has additionally been found that alternatively and more preferably, such responsiveness may be judged, for example, by treating a sample of human peripheral blood mononuclear cells *in vitro* with a Type 1 interferon and looking for upregulation or downregulation of an expression product, preferably mRNA, corresponding to the same gene.

According to a first aspect of the invention, there is thus provided an isolated polypeptide comprising;

(i) the amino acid sequence of SEQ ID NO: 2, SEQ ID NO:4, SEQ ID NO:6 or SEQ ID NO: 8;

(ii) a variant thereof having substantially similar function, e.g. an immunomodulatory activity and/or an anti-viral activity and/or an anti-tumour activity; or

(iii) a fragment of (i) or (ii) which retains substantially similar function, e.g. an immunomodulatory activity and/or an anti-viral activity and/or an anti-tumour activity

for use in therapeutic treatment of a human or non-human animal, more particularly for use as an anti-viral, anti-tumour or immunomodulatory agent. As indicated above, such use may extend to any Type 1 interferon treatable disease.

According to another aspect of the invention, there is provided an isolated polynucleotide, e.g. in the form of an expression vector, which directs expression *in vivo* of a polypeptide as defined above for use in therapeutic treatment of a human or non-human animal, more particularly for use as an anti-viral, anti-tumour or immunomodulatory agent. Such a polynucleotide will typically include a sequence comprising:

(a) the nucleic acid of SEQ. ID. NO: 1, SEQ ID NO: 3, SEQ ID NO: 5 or SEQ ID NO: 7 or the coding sequence thereof;

(b) a sequence which hybridises, e.g. under stringent conditions, to a sequence complementary to a sequence as defined in (a);

(c) a sequence that is degenerate as a result of the genetic code to a sequence as defined in (a) or (b); or

(d) a sequence having at least 60% identity to a sequence as defined in (a), (b) or (c);

such that the polypeptide encoded by said sequence is capable of expression *in vivo*.

In a further aspect, the invention provides a method of predicting responsiveness of a patient to treatment with a Type 1 interferon, e.g. IFN-α treatment (such as IFN-α treatment by the oromucosal route or a parenteral route, for example, intravenously, subcutaneously or intramuscularly), which comprises determining the level of one or more proteins selected from the proteins defined by the sequences set forth in SEQ ID NO: 2, SEQ ID NO:4, SEQ ID NO:6 or SEQ ID NO: 8, and naturally-occurring variants thereof, e.g. allelic variants, or one or more of the corresponding mRNAs, in a cell sample from said patient, e.g. a blood sample,

wherein said sample is obtained from said patient following administration of a Type 1 interferon, e.g. IFN-α by an oromucosal route or intravenously, or is treated prior to said determining with a Type 1 interferon such as IFN-α *in vitro*. Such determining may be combined with determination of any other protein or mRNA whose expression is known to be affected in human cells by Type 1 interferon administration e.g. IFN-α administration.

The invention also provides:

- a pharmaceutical composition comprising the protein defined by the amino acid sequence set forth in SEQ ID NO: 2, SEQ ID NO:4, SEQ ID NO:6 or SEQ ID NO: 8, or a functional variant thereof as defined above, and a pharmaceutically acceptable carrier or diluent:
- a method of treating a subject having a Type 1 interferon treatable disease, which method comprises administering to the said patient an effective amount of such a protein;
- use of such a protein in the manufacture of a medicament for use in therapy as an anti-viral or anti-tumour or immunomodulatory agent, more particularly for use in treatment of a Type 1 interferon treatable disease;
- a pharmaceutical composition comprising a polynucleotide as defined above and a pharmaceutically acceptable carrier or diluent:
- a method of treating a subject having a Type 1 interferon treatable disease, which method comprises administering to said patient an effective amount of such a polynucleotide;
- use of such a polynucleotide in the manufacture of a medicament, e.g. a vector preparation, for use in therapy as an anti-viral, anti-tumour or immunomodulatory agent, more particularly for use in treating a Type 1 interferon treatable disease;
- a polynucleotide capable of expressing *in vivo* an antisense sequence to a coding sequence for the amino acid sequence defined by SEQ ID NO: 2, SEQ ID NO:4, SEQ ID NO:6 or SEQ ID NO: 8, or a naturally-occurring variant of said coding sequence, for use in therapeutic

treatment of a human or non-human animal and pharmaceutical compositions comprising such a polynucleotide in combination with a pharmaceutically acceptable carrier or diluent;

- an antibody to the protein defined by the amino acid sequence set forth the in SEQ ID NO: 2, SEQ ID NO:4, SEQ ID NO:6 or SEQ ID NO: 8 for use in therapeutic treatment of a human or animal body and corresponding pharmaceutical compositions.

Brief description of the Sequences

SEQ. ID. No.1 is the amino acid sequence of human protein HuIFRG-1 and its encoding cDNA.

SEQ. ID. No.2 is the amino acid sequence alone of HuIFRG-1 protein.

SEQ. ID. No.3 is the amino acid sequence of human protein HuIFRG-2 and its encoding cDNA.

SEQ. ID. No.4 is the amino acid sequence alone of HuIFRG-2 protein.

SEQ. ID. No.5 is the amino acid sequence of human protein HuIFRG-3 and its encoding cDNA.

SEQ. ID. No.6 is the amino acid sequence alone of HuIFRG-3 protein.

SEQ. ID. No.7 is the amino acid sequence of human protein HuIFRG-4 and its encoding cDNA.

SEQ. ID. No.8 is the amino acid sequence alone of HuIFRG-4 protein.

Detailed Description of the Invention

As indicated above, human proteins HuIFRG-1, HuIFRG-2, HuIFRG-3 or HuIFRG-4 and functional variants thereof are now envisaged as therapeutically useful agents, more particularly for use as an anti-viral, anti-tumour or immunomodulatory agent.

A variant of HuIFRG-1, HuIFRG-2, HuIFRG-3 or HuIFRG-4 protein for this purpose may be a naturally-occurring variant, either an allelic variant or a species

variant, which has substantially the same functional activity as HuIFRG-1, HuIFRG-2, HuIFRG-3 or HuIFRG-4 protein and is also upregulated in response to administration of IFN-α, e.g oromucosal or intravenous administration of IFN-α. Alternatively, a variant of HuIFRG-1, HuIFRG-2, HuIFRG-3 or HuIFRG-4 protein for therapeutic use may comprise a sequence which varies from SEQ. ID. No. 2 but which is a non-natural mutant.

The term " functional variant" refers to a polypeptide which has the same essential character or basic function of HuIFRG-1, HuIFRG-2, HuIFRG-3 or HuIFRG-4 protein. The essential character of HuIFRG-1, HuIFRG-2, HuIFRG-3 or HuIFRG-4 protein may be deemed to be as an immunomodulatory polypeptide. A functional variant polypeptide may show additionally or alternatively anti-viral activity and/or anti-tumour activity.

Desired anti-viral activity may, for example, be tested for as follows. A sequence encoding a variant to be tested is cloned into a retroviral vector such as a retroviral vector derived from the Moloney murine leukemia virus (MoMuLV) containing the viral packaging signal ψ, and a drug-resistance marker. A pantropic packaging cell line containing the viral *gag*, and *pol*, genes is then co-transfected with the recombinant retroviral vector and a plasmid, pVSV-G, containing the vesicular stomatitis virus envelope glycoprotein in order to produce high-titre infectious replication-incompetent virus (Burns *et al.*, Proc. Natl.. Acad. Sci. USA **84**, 5232-5236). The infectious recombinant virus is then used to transfect interferon sensitive fibroblasts or lymphoblastoid cells and cell lines that stably express the variant protein are then selected and tested for resistance to virus infection in a standard interferon bio-assay (Tovey *et al.*, Nature, **271**, 622-625, 1978). Growth inhibition using a standard proliferation assay (Mosmann, T., J. Immunol. Methods, **65**, 55-63, 1983) and expression of MHC class I and class II antigens using standard techniques may also be determined.

A desired functional variant of HuIFRG-1, HuIFRG-2, HuIFRG-3 or HuIFRG-4 protein may consist essentially of the sequence of SEQ ID NO: 2, SEQ

ID NO: 4, SEQ ID NO: 6 or SEQ ID NO: 8. A functional variant of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6 or SEQ ID NO: 8 may be a polypeptide which has a least 60% to 70% identity, preferably at least 80% or at least 90% and particularly preferably at least 95%, at least 97% or at least 99% identity with the amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6 or SEQ ID NO: 8 over a region of at least 20, preferably at least 30, for instance at least 100 contiguous amino acids or over the full length of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6 or SEQ ID NO: 8. Methods of measuring protein identity are well known in the art.

Amino acid substitutions may be made, for example from 1, 2 or 3 to 10, 20 or 30 substitutions. Conservative substitutions may be made, for example according to the following Table. Amino acids in the same block in the second column and preferably in the same line in the third column may be substituted for each other.

ALIPHATIC	Non-polar	G A P
		I L V
	Polar-uncharged	C S T M
		N Q
	Polar-charged	D E
		K R
AROMATIC		H F W Y

Variant polypeptide sequences for therapeutic use in accordance with the invention may be shorter polypeptide sequences, for example, a peptide of at least 20 amino acids or up to 50, 60, 70, 80, 100, 150 or 200 amino acids in length is

considered to fall within the scope of the invention provided it retains appropriate biological activity of HuIFRG-1, HuIFRG-2, HuIFRG-3 or HuIFRG-4 protein. In particular, but not exclusively, this aspect of the invention encompasses the situation when the variant is a fragment of a complete naturally-occurring protein sequence.

Variant polypeptides for therapeutic use in accordance with the invention may be chemically modified, e.g. post-translationally modified. For example, they may be glycosylated and/or comprise modified amino acid residues. They may also be modified by the addition of a sequence either at the N-terminus and/or C-terminus. Polypeptides for therapeutic use in accordance with the invention may be made synthetically or by recombinant means. Such polypeptides may be modified to include non-naturally occurring amino acids, e.g. D amino acids. Variant polypeptides for use in accordance with the invention may have modifications to increase stability *in vitro* and/or *in vivo*. When the polypeptides are produced by synthetic means, such modifications may be introduced during production. The polypeptides may also be modified following either synthetic or recombinant production.

A number of side chain modifications are known in the protein modification art and may be present in variants for therapeutic use according to the invention. Such modifications include, for example, modifications of amino acids by reductive alkylation by reaction with an aldehyde followed by reduction with $NaBH_4$, amidination with methylacetimidate or acylation with acetic anhydride.

Polypeptides for use in accordance with the invention will be in substantially isolated form. It will be understood that the polypeptides may be mixed with carriers or diluents which will not interfere with the intended purpose of the polypeptide and still be regarded as substantially isolated.

Polynucleotide therapy

As an alternative to administration of HuIFRG-1, HuIFRG-2, HuIFRG-3 or HuIFRG-4 protein, or a functional variant thereof as described above, an isolated polynucleotide may be administered, e.g. in the form of an expression vector such as a viral vector, which directs expression of the desired polypeptide *in vivo*. Hence, as indicated above, in a further embodiment the invention provides an isolated polynucleotide, which directs expression *in vivo* of a polypeptide as defined above, which polynucleotide includes a sequence comprising:

(a) the nucleic acid of SEQ. ID. NO: 1, SEQ ID NO: 3, SEQ ID NO: 5 or SEQ ID NO: 7 or the coding sequence thereof;

(b) a sequence which hybridises, e.g under stringent conditions, to a sequence complementary to a sequence as defined in (a);

(c) a sequence that is degenerate as a result of the genetic code to a sequence as defined in (a) or (b); or

(e) a sequence having at least 60% identity to a sequence as defined in (a), (b) or (c)

for use in therapeutic treatment of a human or non-human animal, more particularly for use as an anti-viral, anti-tumour or immunomodulatory agent.

Preferably, such a polynucleotide will be a DNA. The coding sequence for HuIFRG-1, HuIFRG-2, HuIFRG-3 or HuIFRG-4 protein or a variant thereof may be provided by a cDNA sequence or a genomic DNA sequence. Polynucleotides comprising an appropriate coding sequence can be isolated from human cells or synthesised according to methods well known in the art, as described by way of example in Sambrook *et al.* (1989) Molecular Cloning: A Laboratory Manual, 2nd edition, Cold Spring Harbor Laboratory Press.

Polynucleotides for use in accordance with the invention may include within them synthetic or modified nucleotides. A number of different types of modification to polynucleotides are known in the art. These include methylphosphonate and phosphothioate backbones, addition of acridine or polylysine chains at the 3' and/or 5' ends of the molecule. Such modifications may be incorporated to enhance the *in vivo* activity or life span of the polynucleotide as a therapeutic agent.

Typically, a polynucleotide for use in accordance with the invention will include a sequence of nucleotides, which may preferably be a contiguous sequence of nucleotides, which is capable of hybridising under selective conditions to the complement of the coding sequence of SEQ. ID. NO: 1, SEQ ID NO: 3, SEQ ID NO: 5 or SEQ ID NO: 7. Such hybridisation will occur at a level significantly above background. Background hybridisation may occur, for example, because of other cDNAs present in a cDNA library. The signal level generated by the interaction between a desired coding sequence and the complement of the coding sequence of SEQ. ID. NO: 1, SEQ ID NO: 3, SEQ ID NO: 5 or SEQ ID NO: 7 will typically be at least 10 fold, preferably at least 100 fold, as intense as interactions between other polynucleotides and the target sequence. The intensity of interaction may be measured, for example, by radiolabelling the nucleic acid selected for probing, e.g. with ^{32}P. Selective hybridisation may typically be achieved using conditions of low stringency (0.3M sodium chloride and 0.03M sodium citrate at about 40°C), medium stringency (for example, 0.3M sodium chloride and 0.03M sodium citrate at about 50°C) or high stringency (for example, 0.03M sodium chloride and 0.003M sodium citrate at about 60°C).

The coding sequence of SEQ. ID. NO: 1, SEQ ID NO: 3, SEQ ID NO: 5 or SEQ ID NO: 7 may be modified for incorporation into a polynucleotide as defined above by nucleotide substitutions, for example from 1, 2 or 3 to 10, 25, 50 or 100 substitutions. Degenerate substitutions may, for example, be made and/or substitutions may be made which would result in a conservative amino acid substitution when the modified sequence is translated, for example as shown in the table above. The coding sequence of SEQ. ID. NO: 1, SEQ ID NO: 3, SEQ ID NO: 5 or SEQ ID NO: 7 may alternatively or additionally be modified by one or more insertions and/or deletions and/or by an extension at either or both ends provided it encodes a polypeptide with the appropriate functional activity compared to HuIFRG-1, HuIFRG-2, HuIFRG-3 or HuIFRG-4 protein.

A nucleotide sequence capable of selectively hybridising to the complement of SEQ. ID. NO: 1, SEQ ID NO: 3, SEQ ID NO: 5 or SEQ ID NO: 7, or at least the coding sequence thereof, will be generally at least 70%, preferably at least 80 or 90% and more preferably at least 95% or 97%, homologous to such a DNA sequence. This homology may typically be over a region of at least 20, preferably at least 30, for instance at least 40, 60 or 100 or more contiguous nucleotides of the said DNA sequence.

Any combination of the above mentioned degrees of homology and minimum size may be used to define nucleic acids comprising desired coding sequences, with the more stringent combinations (i.e. higher homology over longer lengths) being preferred. Thus for example a polynucleotide which is at least 80% homologous over 25. preferably over 30 nucleotides may be found suitable, as may be a polynucleotide which is at least 90% homologous over 40 nucleotides.

Homologues of polynucleotide or protein sequences as referred to herein may be determined in accordance with well-known means of homology calculation, e.g. protein homology may be calculated on the basis of amino acid identity (sometimes referred to as "hard homology"). For example the UWGCG Package provides the BESTFIT program which can be used to calculate homology, for example used on its default settings. (Devereux *et al.* (1984) *Nucleic Acids Research* **12**, p387-395). The PILEUP and BLAST algorithms can be used to calculate homology or line up sequences or to identify equivalent or corresponding sequences, typically used on their default settings, for example as described in Altschul S. F. (1993) J Mol Evol **36**:290-300; Altschul, S, F *et al.* (1990) J Mol Biol **215**:403-10.

Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/). This algorithm involves first identifying high scoring sequence pair (HSPs) by identifying short words of length W in the query sequence that either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighbourhood word score threshold

(Altschul *et al*, supra). These initial neighbourhood word hits act as seeds for initiating searches to find HSP=s containing them. The word hits are extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Extensions for the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment. The BLAST program uses as defaults a word length (W) of 11, the BLOSUM62 scoring matrix (see Henikoff and Henikoff (1992) *Proc. Natl. Acad. Sci.* USA 89: 10915-10919) alignments (B) of 50, expectation (E) of 10, M=5, N=4, and a comparison of both strands.

The BLAST algorithm performs a statistical analysis of the similarity between two sequences; see e.g., Karlin and Altschul (1993) *Proc. Natl. Acad. Sci.* USA 90: 5873-5787. One measure of similarity provided by the BLAST algorithm is the smallest sum probability (P(N)), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a sequence is considered similar to another sequence if the smallest sum probability in comparison of the first sequence to the second sequence is less than about 1, preferably less than about 0.1, more preferably less than about 0.01, and most preferably less than about 0.001.

As indicated above, a polynucleotide for use in accordance with the invention in substitution for direct administration of HuIFRG-1, HuIFRG-2, HuIFRG-3 or HuIFRG-4 protein or a functional variant thereof may preferably be in the form of an expression vector. Expression vectors are routinely constructed in the art of molecular biology and may, for example, involve the use of plasmid DNA and appropriate initiators, promoters, enhancers and other elements, such as for example polyadenylation signals which may be necessary, and which are positioned in the correct orientation, in order to allow for protein expression. Such vectors may be viral vectors. Examples of suitable viral vectors include herpes simplex viral vectors,

replication-defective retroviruses, including lentiviruses, adenoviruses, adeno-associated virus, HPV viruses (such as HPV-16 and HPV-18) and attenuated influenza virus vectors. Other suitable vectors would be apparent to persons skilled in the art. By way of further example in this regard reference is made again to Sambrook *et al.*, 1989 (supra).

A polynucleotide capable of expressing *in vivo* an antisense sequence to a coding sequence for the amino acid sequence defined by SEQ. ID. No. 2, or a naturally-occurring variant thereof, for use in therapeutic treatment of a human or non-human animal is also envisaged as constituting an additional aspect of the invention. Again, such a polynucleotide may preferably be in the form of an expression vector. Such a polynucleotide will find use in treatment of diseases associated with upregulation of HuIFRG-1, HuIFRG-2, HuIFRG-3 or HuIFRG-4 protein.

It will be appreciated that antibodies to HuIFRG-1, HuIFRG-2, HuIFRG-3 or HuIFRG-4 protein and antigen-binding fragments thereof may find similar use.

Pharmaceutical compositions

A polypeptide for use in accordance with the invention is typically formulated for administration with a pharmaceutically acceptable carrier or diluent. The pharmaceutical carrier or diluent may be, for example, an isotonic solution. For example, solid oral forms may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate and or polyethelene glycols; binding agents, e.g. starches, arabic gums, gelatin, methyl cellulose, carboxymethylcellulose or polyvinyl pyrrolidone; desegregating agents, e.g. starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents, such as lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Such pharmaceutical preparations may be manufactured in known

manner, for example, by means of mixing, granulating, tableting, sugar-coating, or film coating processes.

Liquid dispersions for oral administration may be syrups, emulsions and suspensions. The syrups may contain as carriers, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol.

Suspensions and emulsions may contain as carrier, for example a natural gum, agar, sodium alginate, pectin, methyl cellulose, carboxymethylcellulose, or polyvinyl alcohol. The suspensions or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and if desired, a suitable amount of lidocaine hydrochloride.

Solutions for intravenous injection or infusions may contain as carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions.

The dose of polypeptide for use in accordance with the invention may be determined according to various parameters, especially according to the substance used; the age, weight and condition of the patient to be treated; the route of administration; and the required regimen. A physician will be able to determine the required route of administration and dosage for any particular patient. A typical daily dose is from about 0.1 to 50 mg per kg, preferably from about 0.1mg/kg to 10mg/kg of body weight, according to the activity of the specific active compound, the age, weight and condition of the subject to be treated, and the frequency and route of administration. Preferably, daily dosage levels are from 5 mg to 2 g.

A polynucleotide for use in accordance with the invention will also typically be formulated for administration with a pharmaceutically acceptable carrier or diluent. Such a polynucleotide may be administered by any known technique whereby expression of the desired polypeptide can be attained *in vivo*. For example,

the polynucleotide may be delivered intradermally, subcutaneously, or intramuscularly. Alternatively, the polynucleotide may be delivered across the skin using a particle-mediated delivery device. A polynucleotide for use in accordance with the invention may be administered by intranasal or oral administration.

A non-viral vector for use in accordance with the invention may be packaged into liposomes or into surfactant. Uptake of nucleic acid constructs for use in accordance with the invention may be enhanced by several known transfection techniques, for example those including the use of transfection agents. Examples of these agents include cationic agents, for example calcium phosphate and DEAE dextran and lipofectants, for example lipophectam and transfectam. The dosage of the nucleic acid to be administered can be varied. Typically, the nucleic acid is administered in the range of from 1pg to 1mg, preferably from 1pg to 10□g nucleic acid for particle-mediated gene delivery and from 10□g to 1 mg for other routes.

Prediction of Type 1 interferon responsiveness

As also indicated above, in a still further aspect the present invention provides a method of predicting responsiveness of a patient to treatment with a Type 1 interferon, e.g. IFN-α treatment such as IFN-α treatment by an oromucosal route or intravenously, which comprises determining the level of one or more of HuIFRG-1, HuIFRG-2, HuIFRG-3, HuIFRG-4 protein and naturally-occurring variants thereof, or one or more corresponding mRNAs, in a cell sample from said patient, wherein said sample is taken from said patient following administration of a Type 1 interferon or is treated prior to said determining with a Type 1 interferon *in vitro*.

Preferably, the Type 1 interferon for testing responsiveness will be the Type 1 interferon selected for treatment. It may be administered by the proposed treatment route and at the proposed treatment dose. Preferably, the subsequent sample analysed may be, for example, a blood sample or a sample of peripheral blood mononuclear cells (PBMCs) isolated from a blood sample.

More conveniently and preferably, a sample obtained from the patient comprising PBMCs isolated from blood may be treated *in vitro* with a Type 1 interferon, e.g. at a dosage range of about 1 to 10,000 IU/ml. Such treatment may be for a period of hours, e.g. about 7 to 8 hours. Preferred treatment conditions for such *in vitro* testing may be determined by testing PBMCs taken from normal donors with the same interferon and looking for upregulation of an appropriate expression product. Again, the Type 1 interferon employed will preferably be the Type 1 interferon proposed for treatment of the patient, e.g. recombinant IFN-α. PBMCs for such testing may be isolated in conventional manner from a blood sample using Ficoll-Hypaque density gradients. An example of a suitable protocol for such *in vitro* testing of Type 1 interferon responsiveness is provided in Example 6 below.

The sample, if appropriate after *in vitro* treatment with a Type 1 interferon, may be analysed for the level of HuIFRG-1, HuIFRG-2, HuIFRG-3 or HuIFRG-4 protein or a naturally-occurring variant thereof. This may be done using an antibody or antibodies capable of specifically binding one or more of HuIFRG-1, HuIFRG-2, HuIFRG-3 or HuIFRG-4 protein and naturally-occurring variants thereof, eg. allelic variants thereof. Preferably, however, the sample will be analysed for mRNA encoding HuIFRG-1, HuIFRG-2, HuIFRG-3 or HuIFRG-4 protein or a naturally-occurring variant thereof. Such mRNA analysis may employ any of the techniques known for detection of mRNAs, e.g. Northern blot detection or mRNA differential display. A variety of known nucleic acid amplification protocols may be employed to amplify any mRNA of interest present in the sample, or a portion thereof, prior to detection. The mRNA of interest, or a corresponding amplified nucleic acid, may be probed for using a nucleic acid probe attached to a solid support. Such a solid support may be a micro-array carrying probes to determine the level of further mRNAs or amplification products thereof corresponding to Type 1 interferon upregulated genes, e.g. such genes identified as upregulated in response to oromucosal or intravenous administration of IFN-α. Methods for constructing such micro-arrays (also referred to commonly as nucleic acid, probe or DNA chips) are well-known (see, for example, EP-B 0476014 and 0619321 of Affymax

Technologies N.V. and Nature Genetics Supplement January 1999 entitled "The Chipping Forecast").

The following examples illustrate the invention:

Examples

Example 1

Previous experiments had shown that the application of 5 µl of crystal violet to each nostril of a normal adult mouse using a P20 Eppendorf micropipette resulted in an almost immediate distribution of the dye over the whole surface of the oropharyngeal cavity. Staining of the oropharyngeal cavity was still apparent some 30 minutes after application of the dye. These results were confirmed by using ^{125}I-labelled recombinant human IFN-□1-8 applied in the same manner. The same method of administration was employed to effect oromucosal administration in the studies which are described below.

Six week old, male DBA/2 mice were treated with either 100,000 IU of recombinant murine interferon α (IFN α) purchased from Life Technologies Inc, in phosphate buffered saline (PBS), 10µg of recombinant human interleukin 15 (IL-15) purchased from Protein Institute Inc, PBS containing 100 µg/ml of bovine serum albumin (BSA), or left untreated. Eight hours later, the mice were sacrificed by cervical dislocation and the lymphoid tissue was removed surgically from the oropharyngeal cavity and snap frozen in liquid nitrogen and stored at -80°C. RNA was extracted from the lymphoid tissue by the method of Chomczynski and Sacchi (Anal. Biochem. (1987) **162**, 156-159) and subjected to mRNA Differential Display Analysis (Lang, P. and Pardee, A.B., Science, **257**, 967-971).

Differential Display Analysis

Differential display analysis was carried out using the "Message Clean" and

"RNA image" kits of the GenHunter Corporation essentially as described by the manufacturer. Briefly, RNA was treated with RNase-free DNase, and 1 µg was reverse-transcribed in 100 µl of reaction buffer using either one or the other of the three one-base anchored oligo-(dT) primers A, C, or G. RNA was also reverse-transcribed using one or the other of the 9 two-base anchored oligo-(dT) primers AA, CC, GG, AC, CA, GA, AG, CG, GC. All the samples to be compared were reverse transcribed in the same experiment, separated into aliquots and frozen. The amplification was performed with only 1 µl of the reverse transcription sample in 10 µl of amplification mixture containing *Taq* DNA polymerase and α- ^{33}P dATP (3,000 Ci/mmole). Eighty 5' end (HAP) random sequence primers were used in combination with each of the (HT11) A, C, G, AA, CC, GG, AC, CA, GA, AG, CG or GC primers. Samples were then run on 7% denaturing polyacrylamide gels and exposed to authoradiography. Putative differentially expressed bands were cut out, reamplified according to the instructions of the supplier, and further used as probes to hybridise Northern blots of RNA extracted from the oropharyngeal cavity of IFN treated, IL-15 treated, and excipient treated animals.

Cloning and Sequencing

Re-amplified bands from the differential display screen were cloned in the *Sfr* I site of the pPCR-Script SK(+) plasmid (Stratagene), and cDNA amplified from the rapid amplification of cDNA ends were isolated by TA cloning in the pCR3 plasmid (Invitrogen). DNA was sequenced using an automatic di-deoxy sequencer (Perkin Elmer ABI PRISM 377).

Identification of Human cDNA

Differentially expressed murine 3' sequences identified from the differential display screen were compared with random human expressed sequence tags (EST) present in the dbEST database of GenBank™ of the United States National Center for Biotechnology Information (NCBI). The sequences potentially related to the murine EST isolated from the differential display screen were combined in a contig and used

to construct a human consensus sequence corresponding to a putative cDNA.

One such cDNA was found to correspond to GenBank cDNA sequence g4586459. The corresponding polypeptide sequence is GenBank sequence g4586460, not assigned in GenBank any function.

Other mouse genes upregulated in lymphoid tissue in response to oromucosal administration of IFN-α as described above have also been found to be upregulated in the spleen of mice in response to intravenous administration of IFN-α. A similar result is anticipated in respect of the mouse gene corresponding to the human gene identified by Genbank cDNA accesssion no. g4586459 when intravenous administration of IFN-α is carried out as described in Example 5 below.

Furthermore, mRNAs corresponding to human gene analogues of mouse genes found to be upregulated in response to oromucosal and intravenous administration of IFN-α have been found to be enhanced in human peripheral blood mononuclear cells following treatment with IFN-α *in vitro*. The same result is anticipated for mRNA corresponding to the cDNA as set forth in SEQ ID NO: 1 when human peripheral blood mononuclear cells are treated with IFN-α as described in Example 6 below.

Example 2

Previous experiments had shown that the application of 5 µl of crystal violet to each nostril of a normal adult mouse using a P20 Eppendorf micropipette resulted in an almost immediate distribution of the dye over the whole surface of the oropharyngeal cavity. Staining of the oropharyngeal cavity was still apparent some 30 minutes after application of the dye. These results were confirmed by using ^{125}I-labelled recombinant human IFN-□1-8 applied in the same manner. The same method of administration was employed to effect oromucosal administration in the studies which are described below.

Six week old, male DBA/2 mice were treated with either 100,000 IU of recombinant murine interferon α (IFN α) purchased from Life Technologies Inc, in phosphate buffered saline (PBS), 10μg of recombinant human interleukin 15 (IL-15) purchased from Protein Institute Inc, PBS containing 100 μg/ml of bovine serum albumin (BSA), or left untreated. Eight hours later, the mice were sacrificed by cervical dislocation and the lymphoid tissue was removed surgically from the oropharyngeal cavity and snap frozen in liquid nitrogen and stored at -80°C. RNA was extracted from the lymphoid tissue by the method of Chomczynski and Sacchi (Anal. Biochem. (1987) **162**, 156-159) and subjected to mRNA Differential Display Analysis (Lang, P. and Pardee, A.B., Science, **257**, 967-971).

Differential Display Analysis

Differential display analysis was carried out using the "Message Clean" and "RNA image" kits of the GenHunter Corporation essentially as described by the manufacturer. Briefly, RNA was treated with RNase-free DNase, and 1 μg was reverse-transcribed in 100 μl of reaction buffer using either one or the other of the three one-base anchored oligo-(dT) primers A, C, or G. RNA was also reverse-transcribed using one or the other of the 9 two-base anchored oligo-(dT) primers AA, CC, GG, AC, CA, GA, AG, CG, GC. All the samples to be compared were reverse transcribed in the same experiment, separated into aliquots and frozen. The amplification was performed with only 1 μl of the reverse transcription sample in 10 μl of amplification mixture containing *Taq* DNA polymerase and α-^{33}P dATP (3,000 Ci/mmole). Eighty 5' end (HAP) random sequence primers were used in combination with each of the (HT11) A, C, G, AA, CC, GG, AC, CA, GA, AG, CG or GC primers. Samples were then run on 7% denaturing polyacrylamide gels and exposed to authoradiography. Putative differentially expressed bands were cut out, reamplified according to the instructions of the supplier, and further used as probes to hybridise Northern blots of RNA extracted from the oropharyngeal cavity of IFN treated, IL-15 treated, and excipient treated animals.

Cloning and Sequencing

Re-amplified bands from the differential display screen were cloned in the *Sfi* 1 site of the pPCR-Script SK(+) plasmid (Stratagene), and cDNA amplified from the rapid amplification of cDNA ends were isolated by TA cloning in the pCR3 plasmid (Invitrogen). DNA was sequenced using an automatic di-deoxy sequencer (Perkin Elmer ABI PRISM 377).

Identification of Human cDNA

Differentially expressed murine 3' sequences identified from the differential display screen were compared with random human expressed sequence tags (EST) present in the dbEST database of GenBank™ of the United States National Center for Biotechnology Information (NCBI). The sequences potentially related to the murine EST isolated from the differential display screen were combined in a contig and used to construct a human consensus sequence corresponding to a putative cDNA.

One such cDNA was found to correspond to GenBank cDNA sequence g2342476. The corresponding polypeptide sequence is GenBank sequence g2342477, not assigned in GenBank any function.

Other mouse genes upregulated in lymphoid tissue in response to oromucosal administration of IFN-α as described above have also been found to be upregulated in the spleen of mice in response to intravenous administration of IFN-α. A similar result is anticipated in respect of the mouse gene corresponding to the human gene identified by Genbank cDNA accesssion no. g2342476 when intravenous administration of IFN-α is carried out as described in Example 5 below.

Furthermore, mRNAs corresponding to human gene analogues of mouse genes found to be upregulated in response to oromucosal and intravenous administration of IFN-α have been found to be enhanced in human peripheral blood mononuclear cells following treatment with IFN-α *in vitro*. The same result is

anticipated for mRNA corresponding to the cDNA as set forth in SEQ. ID. No. 3 when human peripheral blood mononuclear cells are treated with IFN-α as described in Example 6 below.

Example 3

Previous experiments had shown that the application of 5 µl of crystal violet to each nostril of a normal adult mouse using a P20 Eppendorf micropipette resulted in an almost immediate distribution of the dye over the whole surface of the oropharyngeal cavity. Staining of the oropharyngeal cavity was still apparent some 30 minutes after application of the dye. These results were confirmed by using ^{125}I-labelled recombinant human IFN-□1-8 applied in the same manner. The same method of administration was employed to effect oromucosal administration in the studies which are described below.

Six week old, male DBA/2 mice were treated with either 100,000 IU of recombinant murine interferon α (IFN α) purchased from Life Technologies Inc, in phosphate buffered saline (PBS), 10µg of recombinant human interleukin 15 (IL-15) purchased from Protein Institute Inc, PBS containing 100 µg/ml of bovine serum albumin (BSA), or left untreated. Eight hours later, the mice were sacrificed by cervical dislocation and the lymphoid tissue was removed surgically from the oropharyngeal cavity and snap frozen in liquid nitrogen and stored at -80°C. RNA was extracted from the lymphoid tissue by the method of Chomczynski and Sacchi (Anal. Biochem. (1987) **162**, 156-159) and subjected to mRNA Differential Display Analysis (Lang, P. and Pardee, A.B., Science, **257**, 967-971).

Differential Display Analysis

Differential display analysis was carried out using the "Message Clean" and "RNA image" kits of the GenHunter Corporation essentially as described by the manufacturer. Briefly, RNA was treated with RNase-free DNase, and 1 µg was reverse-transcribed in 100 µl of reaction buffer using either one or the other of the

three one-base anchored oligo-(dT) primers A, C, or G. RNA was also reverse-transcribed using one or the other of the 9 two-base anchored oligo-(dT) primers AA, CC, GG, AC, CA, GA, AG, CG, GC. All the samples to be compared were reverse transcribed in the same experiment, separated into aliquots and frozen. The amplification was performed with only 1 µl of the reverse transcription sample in 10 µl of amplification mixture containing *Taq* DNA polymerase and α-^{33}P dATP (3,000 Ci/mmole). Eighty 5' end (HAP) random sequence primers were used in combination with each of the (HT11) A, C, G, AA, CC, GG, AC, CA, GA, AG, CG or GC primers. Samples were then run on 7% denaturing polyacrylamide gels and exposed to authoradiography. Putative differentialiy expressed bands were cut out, reamplified according to the instructions of the supplier, and further used as probes to hybridise Northern blots of RNA extracted from the oropharyngeal cavity of IFN treated, IL-15 treated, and excipient treated animals.

Cloning and Sequencing

Re-amplified bands from the differential display screen were cloned in the *Sfr* 1 site of the pPCR-Script SK(+) plasmid (Stratagene), and cDNA amplified from the rapid amplification of cDNA ends were isolated by TA cloning in the pCR3 plasmid (Invitrogen). DNA was sequenced using an automatic di-deoxy sequencer (Perkin Elmer ABI PRISM 377).

Identification of Human cDNA

Differentially expressed murine 3' sequences identified from the differential display screen were compared with random human expressed sequence tags (EST) present in the dbEST database of GenBank™ of the United States National Center for Biotechnology Information (NCBI). The sequences potentially related to the murine EST isolated from the differential display screen were combined in a contig and used to construct a human consensus sequence corresponding to a putative cDNA.

One such cDNA was found to correspond to GenBank cDNA sequence

g3327161. The corresponding polypeptide sequence is GenBank sequence g3327162, not assigned in GenBank any function.

Other mouse genes upregulated in lymphoid tissue in response to oromucosal administration of IFN-α as described above have also been found to be upregulated in the spleen of mice in response to intravenous administration of IFN-α. A similar result is anticipated in respect of the mouse gene corresponding to the human gene identified by Genbank cDNA accesssion no. g3327161 when intravenous administration of IFN-α is carried out as described in Example 5 below.

Furthermore, mRNAs corresponding to human gene analogues of mouse genes found to be upregulated in response to oromucosal and intravenous administration of IFN-α have been found to be enhanced in human peripheral blood mononuclear cells following treatment with IFN-α *in vitro*. The same result is anticipated for mRNA corresponding to the cDNA as set forth in SEQ. ID. No. 5 when human peripheral blood mononuclear cells are treated with IFN-α as described in Example 6 below.

Example 4

Previous experiments had shown that the application of 5 µl of crystal violet to each nostril of a normal adult mouse using a P20 Eppendorf micropipette resulted in an almost immediate distribution of the dye over the whole surface of the oropharyngeal cavity. Staining of the oropharyngeal cavity was still apparent some 30 minutes after application of the dye. These results were confirmed by using ^{125}I-labelled recombinant human IFN-□1-8 applied in the same manner. The same method of administration was employed to effect oromucosal administration in the studies which are described below.

Six week old, male DBA/2 mice were treated with either 100,000 IU of recombinant murine interferon α (IFN α) purchased from Life Technologies Inc, in phosphate buffered saline (PBS), 10µg of recombinant human interleukin 15 (IL-15)

purchased from Protein Institute Inc, PBS containing 100 µg/ml of bovine serum albumin (BSA), or left untreated. Eight hours later, the mice were sacrificed by cervical dislocation and the lymphoid tissue was removed surgically from the oropharyngeal cavity and snap frozen in liquid nitrogen and stored at -80°C. RNA was extracted from the lymphoid tissue by the method of Chomczynski and Sacchi (Anal. Biochem. (1987) **162**, 156-159) and subjected to mRNA Differential Display Analysis (Lang, P. and Pardee, A.B., Science, **257**, 967-971).

Differential Display Analysis

Differential display analysis was carried out using the "Message Clean" and "RNA image" kits of the GenHunter Corporation essentially as described by the manufacturer. Briefly, RNA was treated with RNase-free DNase, and 1 µg was reverse-transcribed in 100 µl of reaction buffer using either one or the other of the three one-base anchored oligo-(dT) primers A, C, or G. RNA was also reverse-transcribed using one or the other of the 9 two-base anchored oligo-(dT) primers AA, CC, GG, AC, CA, GA, AG, CG, GC. All the samples to be compared were reverse transcribed in the same experiment, separated into aliquots and frozen. The amplification was performed with only 1 µl of the reverse transcription sample in 10 µl of amplification mixture containing *Taq* DNA polymerase and α-^{33}P dATP (3,000 Ci/mmole). Eighty 5' end (HAP) random sequence primers were used in combination with each of the (HT11) A, C, G, AA, CC, GG, AC, CA, GA, AG, CG or GC primers. Samples were then run on 7% denaturing polyacrylamide gels and exposed to authoradiography. Putative differentially expressed bands were cut out, reamplified according to the instructions of the supplier, and further used as probes to hybridise Northern blots of RNA extracted from the oropharyngeal cavity of IFN treated, IL-15 treated, and excipient treated animals.

Cloning and Sequencing

Re-amplified bands from the differential display screen were cloned in the

Sfr 1 site of the pPCR-Script SK(+) plasmid (Stratagene), and cDNA amplified from the rapid amplification of cDNA ends were isolated by TA cloning in the pCR3 plasmid (Invitrogen). DNA was sequenced using an automatic di-deoxy sequencer (Perkin Elmer ABI PRISM 377).

Identification of Human cDNA

Differentially expressed murine 3' sequences identified from the differential display screen were compared with random human expressed sequence tags (EST) present in the dbEST database of GenBank™ of the United States National Center for Biotechnology Information (NCBI). The sequences potentially related to the murine EST isolated from the differential display screen were combined in a contig and used to construct a human consensus sequence corresponding to a putative cDNA.

One such cDNA was found to correspond to GenBank cDNA sequence g4529886. The corresponding polypeptide sequence is GenBank sequence g4529888, not assigned in GenBank any function.

Other mouse genes upregulated in lymphoid tissue in response to oromucosal administration of IFN-α as described above have also been found to be upregulated in the spleen of mice in response to intravenous administration of IFN-α. A similar result is anticipated in respect of the mouse gene corresponding to the human gene identified by Genbank cDNA accesssion no. g4529886 when intravenous administration of IFN-α is carried out as described in Example 5 below.

Furthermore, mRNAs corresponding to human gene analogues of mouse genes found to be upregulated in response to oromucosal and intravenous administration of IFN-α have been found to be enhanced in human peripheral blood mononuclear cells following treatment with IFN-α *in vitro*. The same result is anticipated for mRNA corresponding to the cDNA as set forth in SEQ. ID. No. 7 when human peripheral blood mononuclear cells are treated with IFN-α as described in Example 6 below.

Example 5

Intravenous administration of IFN-α

Male DBA/2 mice are injected intravenously with 100,000 IU of recombinant murine IFN-α purchased from Life Technologies Inc. in 200 µl of PBS or treated with an equal volume of PBS alone. Eight hours later the animals are sacrificed by cervical dislocation and the spleen was removed using conventional procedures. Total RNA was extracted by the method of Chomczynski and Sacchi (Anal. Biochem. (1987) 162, 156-159) and 10.0 µg of total RNA per sample is subjected to Northern blotting in the presence of glyoxal and hybridised with a cDNA probe for the mRNA of interest as described by Dandoy-Dron et al. (J. Biol. Chem. (1998) 273, 7691-7697). The blots are first exposed to autoradiography and then quantified using a Phospholmager according to the manufacturer's instructions.

Example 6

Testing Type 1 interferon responsiveness *in vitro*

Human peripheral blood mononuclear cells (PBMC) from normal donors are isolated on Ficoll-Hypaque density gradients and treated *in vitro* with 10,000 IU of recombinant human IFN-α2 (intron A from Schering-Plough) in PBS or with an equal volume of PBS alone. Eight hours later the cells are centrifuged (800 x g for 10 minutes) and the cell pellet recovered. Total RNA is extracted from the cell pellet by the method of Chomczynski and Sacchi and 10.0 µg of total RNA per sample is subjected to Northern blotting as described in Example 5 above.

The same procedure can be used to predict Type 1 interferon responsiveness using PBMC taken from a patient proposed to be treated with a Type 1 interferon.

CLAIMS:

1. An isolated polypeptide comprising

   (i) the amino acid sequence of any one of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6 or SEQ ID NO: 8;

   (ii) a variant thereof having substantially similar function selected from immunomodulatory activity and/or anti-viral activity and/or anti-tumour activity; or

   (iii) a fragment of a sequence as defined in (i) or (ii) which retains substantially similar function selected from immmunomodulatory activity and/or anti-viral activity and/or anti-tumour activity

   for use in therapeutic treatment of a human or non-human animal.

2. An isolated polynucleotide which directs expression *in vivo* of a polypeptide as defined in claim 1 for use in therapeutic treatment of a human or non-human animal.

3. An isolated polynucleotide as claimed in claim 2 which includes a sequence comprising:

   (a) the nucleic acid of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5 or SEQ ID NO: 7 or the coding sequence thereof;

   (b) a sequence which hybridises to a sequence complementary to a sequence as defined in (a);

   (c) a sequence which is degenerate as a result of the genetic code to a sequence as defined in (a) or (b);or

   (d) a sequence having at least 60% identity to a sequence as defined in (a), (b) or (c);

   such that the polypeptide encoded by said sequence is capable of expression *in vivo*.

4. A polypeptide or polynucleotide as claimed in any one of claims 1 to 3 for use as an anti-viral, anti-tumour or immunomodulatory agent.

5. A polypeptide or polynucleotide as claimed in claim 4 for use in treating a Type 1 interferon treatable disease.

6. A pharmaceutical composition comprising a polypeptide or polynucleotide as claimed in any one of claims 1 to 5 and a pharmaceutically acceptable carrier or diluent.

7. Use of a polypeptide or polynucleotide as defined in any one of claims 1 to 5 in the preparation of a medicament for use in therapy as an anti-viral, anti-tumour or immunomodulatory agent.

8. A method of treating a patient having a Type 1 interferon treatable disease, which comprises administering to said patient an effective amount of a polypeptide or polynucleotide as defined in any one of claims 1 to 5.

9. A method of predicting responsiveness of a patient to treatment with a Type 1 interferon, which comprises determining the level of one or more proteins selected from the proteins defined by the sequences set forth in SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6 or SEQ ID NO: 8 and naturally-occurring variants thereof, or one or more of the corresponding mRNAs, in a cell sample from said patient, wherein said sample is obtained from said patient following administration of a Type 1 interferon or is treated prior to said determining with a Type 1 interferon *in vitro*.

10. A method as claimed in claim 9 wherein the interferon administered prior to obtaining said sample or used to treat said sample *in vitro* is the interferon proposed for treatment.

11. A method as claimed in claim 9 or 10 wherein a sample comprising peripheral blood mononuclear cells isolated from a blood sample of the patient is treated with a Type 1 interferon *in vitro*.

12. A method as claimed in any one of claims 9 to 11 wherein said determining comprises determining the level of mRNA encoding the protein defined by the sequence set forth in SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6 or SEQ ID NO: 8 or a naturally-occurring variant of said protein.

13. A polynucleotide capable of expressing *in vivo* an antisense sequence to a coding sequence for the amino acid sequence defined by SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6 or SEQ ID NO: 8or a naturally-occurring variant of said coding sequence for use in therapeutic treatment of a human or non-human animal.

14. An antibody to the amino acid sequence set forth in SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6 or SEQ ID NO: 8 for use in therapeutic treatment of a human or animal body.

SEQUENCE LISTING

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<221> CDS
<222> (1)..(1407)

<400> 1

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            20                  25                  30

tct gat ggg aca ctc tac tgc cag gtg cct tgt aag ggt ctg aac aag   144
Ser Asp Gly Thr Leu Tyr Cys Gln Val Pro Cys Lys Gly Leu Asn Lys
        35                  40                  45

ctc agt gac ctt cta cgt aag ata gag gac tac ttc cat tgc aag cac   192
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65                  70                  75                  80

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Leu Phe His Cys Lys Gly Lys Trp Leu Arg Val Glu Ile Thr Asn Val
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His Ser Ser Arg Ala Leu Asp Val Gln Phe Leu Asp Ser Gly Thr Val
            100                 105                 110

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Ile His Lys Leu Glu Val Leu Met Glu Glu Met Ile Leu Tyr Tyr Ser
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Leu Val Asn Ile Arg Lys Val Gln Pro Leu Val Asp Met Phe Arg Lys
    370                 375                 380

ctg ccc ttc caa gca gtc aca gct caa ctt gca gga gtg aag tgc aac   1200
Leu Pro Phe Gln Ala Val Thr Ala Gln Leu Ala Gly Val Lys Cys Asn
385                 390                 395                 400

cag tgg tct gag gag gct tct atg gtg ttt cga aat cat gtg gag aag   1248
Gln Trp Ser Glu Glu Ala Ser Met Val Phe Arg Asn His Val Glu Lys
                405                 410                 415

aaa cct ctg gtg gca ctg gtg cag aca gtc att gaa aat gct aac cct   1296
Lys Pro Leu Val Ala Leu Val Gln Thr Val Ile Glu Asn Ala Asn Pro
            420                 425                 430

tgg gac cgg aaa gta gtg gtc tac tta gtg gac aca tcg ttg cca gac   1344
Trp Asp Arg Lys Val Val Val Tyr Leu Val Asp Thr Ser Leu Pro Asp
        435                 440                 445

acc gat acc tgg att cat gat ttt atg tca gag tat ctg ata gag ctt   1392
Thr Asp Thr Trp Ile His Asp Phe Met Ser Glu Tyr Leu Ile Glu Leu
    450                 455                 460

tca aaa gtt aat taa tgactgcctc tgaaaccttg acaactaatt cagatttttt   1447
Ser Lys Val Asn
465

agcaataaca aaatgtagta ggcttaaaaa aaatcttaac tctgctacat ggctctgact 1507

gctgtggggg attgaaaaga atatgcttat gtttgatgaa agatatttaa caagttttgt 1567

tttaacagag ttgacttttc aaagaaaatt gtacttgaat tattactata atattagaat 1627

aaaaatgttt atc                                                    1640
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<210> 2
<211> 469
<212> PRT
<213> Homo sapiens

<400> 2

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Asn Ala Thr Cys Leu Lys Ala Ile Cys Asp Lys Ser Leu Glu Val His
  1               5                  10                  15

Leu Gln Val Asp Ala Met Tyr Thr Asn Val Lys Val Thr Asn Ile Cys
            20                  25                  30

Ser Asp Gly Thr Leu Tyr Cys Gln Val Pro Cys Lys Gly Leu Asn Lys
        35                  40                  45
```

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Leu Ser Asp Leu Leu Arg Lys Ile Glu Asp Tyr Phe His Cys Lys His
 50                  55                  60

Met Thr Ser Glu Cys Phe Val Ser Leu Pro Phe Cys Gly Lys Ile Cys
65                  70                  75                  80

Leu Phe His Cys Lys Gly Lys Trp Leu Arg Val Glu Ile Thr Asn Val
                85                  90                  95

His Ser Ser Arg Ala Leu Asp Val Gln Phe Leu Asp Ser Gly Thr Val
            100                 105                 110

Thr Ser Val Lys Val Ser Glu Leu Arg Glu Ile Pro Pro Arg Phe Leu
        115                 120                 125

Gln Glu Met Ile Ala Ile Pro Pro Gln Ala Ile Lys Cys Cys Leu Ala
    130                 135                 140

Asp Leu Pro Gln Ser Ile Gly Met Trp Thr Pro Asp Ala Val Leu Trp
145                 150                 155                 160

Leu Arg Asp Ser Val Leu Asn Cys Ser Asp Cys Ser Ile Lys Val Thr
                165                 170                 175

Lys Val Asp Glu Thr Arg Gly Ile Ala His Val Tyr Leu Phe Thr Pro
            180                 185                 190

Lys Asn Phe Pro Asp Pro His Arg Ser Ile Asn Arg Gln Ile Thr Asn
        195                 200                 205

Ala Asp Leu Trp Lys His Gln Lys Asp Val Phe Leu Ser Ala Ile Ser
    210                 215                 220

Ser Gly Ala Asp Ser Pro Asn Ser Lys Asn Gly Asn Met Pro Met Ser
225                 230                 235                 240

Gly Asn Thr Gly Glu Asn Phe Arg Lys Asn Leu Thr Asp Val Ile Lys
                245                 250                 255

Lys Ser Met Val Asp His Thr Ser Ala Phe Ser Thr Glu Glu Leu Pro
            260                 265                 270

Pro Pro Val His Leu Ser Lys Pro Gly Glu His Met Asp Val Tyr Val
        275                 280                 285

Pro Val Ala Cys His Pro Gly Tyr Phe Val Ile Gln Pro Trp Gln Glu
    290                 295                 300

Ile His Lys Leu Glu Val Leu Met Glu Glu Met Ile Leu Tyr Tyr Ser
305                 310                 315                 320

Val Ser Glu Glu Arg His Ile Ala Val Glu Lys Asp Gln Val Tyr Ala
                325                 330                 335

Ala Lys Val Glu Asn Lys Trp His Arg Val Leu Leu Lys Gly Ile Leu
            340                 345                 350
```

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Thr Asn Gly Leu Val Ser Val Tyr Glu Leu Asp Tyr Gly Lys His Glu
        355                 360                 365

Leu Val Asn Ile Arg Lys Val Gln Pro Leu Val Asp Met Phe Arg Lys
    370                 375                 380

Leu Pro Phe Gln Ala Val Thr Ala Gln Leu Ala Gly Val Lys Cys Asn
385                 390                 395                 400

Gln Trp Ser Glu Glu Ala Ser Met Val Phe Arg Asn His Val Glu Lys
                405                 410                 415

Lys Pro Leu Val Ala Leu Val Gln Thr Val Ile Glu Asn Ala Asn Pro
            420                 425                 430

Trp Asp Arg Lys Val Val Val Tyr Leu Val Asp Thr Ser Leu Pro Asp
        435                 440                 445

Thr Asp Thr Trp Ile His Asp Phe Met Ser Glu Tyr Leu Ile Glu Leu
    450                 455                 460

Ser Lys Val Asn
465


<210> 3
<211> 1432
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (130)..(810)

<400> 3
ttgcagccgc cggcagctac tgcaaggcaa aagccggagt ggacgtgtct tttgaaactg 60

ctgctctttc acttctcagg cgtcaccgag agctcagcac ccaggctgaa ctctgtacca 120

tttggaaga atg gaa gct gat gca tct gtt gac atg ttt tcc aaa gtc ctg 171
          Met Glu Ala Asp Ala Ser Val Asp Met Phe Ser Lys Val Leu
            1               5                  10

gag cat cag ctg ctt cag act acc aaa ctg gtg gaa gaa cat ttg gat   219
Glu His Gln Leu Leu Gln Thr Thr Lys Leu Val Glu Glu His Leu Asp
 15                 20                  25                  30

tct gaa att caa aaa ctg gat cag atg gat gag gat gaa ttg gaa cgc   267
Ser Glu Ile Gln Lys Leu Asp Gln Met Asp Glu Asp Glu Leu Glu Arg
                35                  40                  45

ctt aaa gaa aag aga ctc cag gca cta agg aaa gct caa cag cag aaa   315
Leu Lys Glu Lys Arg Leu Gln Ala Leu Arg Lys Ala Gln Gln Gln Lys
            50                  55                  60
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caa gaa tgg ctt  t aaa gga cat ggg gaa tac aga gaa atc cct agt   363
Gln Glu Trp Leu  r Lys Gly His Gly Glu Tyr Arg Glu Ile Pro Ser
         65                  70                  75

gaa aga gac ttt ttt caa gaa gtc aag gag agt gaa aat gtg gtt tgc   411
Glu Arg Asp Phe Phe Gln Glu Val Lys Glu Ser Glu Asn Val Val Cys
     80                  85                  90

cat ttc tac aga gac tcc aca ttc agg tgt aaa ata cta gac aga cat   459
His Phe Tyr Arg Asp Ser Thr Phe Arg Cys Lys Ile Leu Asp Arg His
 95                 100                 105                 110

ctg gca ata ttg tcc aag aaa cac ctc gag acc aat ttt ttg aag ctg   507
Leu Ala Ile Leu Ser Lys Lys His Leu Glu Thr Asn Phe Leu Lys Leu
                115                 120                 125

aat gtg gaa aaa gca cct ttc ctt tgt gag aga ctg cat atc aaa gtc   555
Asn Val Glu Lys Ala Pro Phe Leu Cys Glu Arg Leu His Ile Lys Val
            130                 135                 140

att ccc aca cta gca ctg cta aaa gat ggg aaa aca caa gat tat gtt   603
Ile Pro Thr Leu Ala Leu Leu Lys Asp Gly Lys Thr Gln Asp Tyr Val
        145                 150                 155

gtt ggg ttt act gac cta gga aat aca gat gac ttc acc aca gaa act   651
Val Gly Phe Thr Asp Leu Gly Asn Thr Asp Asp Phe Thr Thr Glu Thr
    160                 165                 170

tta gaa tgg agg ctc ggt tct tct gac att ctt aat tac agt gga aat   699
Leu Glu Trp Arg Leu Gly Ser Ser Asp Ile Leu Asn Tyr Ser Gly Asn
175                 180                 185                 190

tta atg gag cca cca ttt cag aac caa aag aaa ttt gga aca aac ttc   747
Leu Met Glu Pro Pro Phe Gln Asn Gln Lys Lys Phe Gly Thr Asn Phe
                195                 200                 205

aca aag ctg gaa aag aaa act atg cga gga aag aaa tat gat tca gac   795
Thr Lys Leu Glu Lys Lys Thr Met Arg Gly Lys Lys Tyr Asp Ser Asp
            210                 215                 220

tct gat gat gat tag agctcaataa ttctttgtaa attgtctttt tttttctgct   850
Ser Asp Asp Asp

tcagatttaa atgtgttttt aaaattctat taatgtctat acattggtca cctaaatact 910

catattctcg agttttatac agttgtatca catcgaaaag tgtctttact gttttctgtg 970

tggccatcat gtttaagttg aggaaactca gttcttaaat tatctgggaa gggtctggat 1030

tctctatttt tgagattgac tttatcacaa tatgattctt acatctttat accatttaca 1090

attgtgtttt agatctacag agttagaaat tcgraaacta ttccaggact aattcttaat 1150

cggcattatt tatacaagag gtcaagtaac atttactagc gcaatactgc acttgtaaat 1210

gaattataaa cgctcttctg gaatatattt aaataaccat taaagaactg cttattcatt 1270
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ctggacactg catgttgatg ttgaatcaac tgatgccagc agaaagctat tttgatttgt 1330

gaacatactg ccttatttaa agggtcctga ttgcttgtat tttaagacat tcattaaaaa 1390

gaaaccagga aacacttttg aaataacagc ataaggaact tc 1432

<210> 4
<211> 226
<212> PRT
<213> Homo sapiens

<400> 4

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Met Glu Ala Asp Ala Ser Val Asp Met Phe Ser Lys Val Leu Glu His
  1               5                  10                  15

Gln Leu Leu Gln Thr Thr Lys Leu Val Glu Glu His Leu Asp Ser Glu
            20                  25                  30

Ile Gln Lys Leu Asp Gln Met Asp Glu Asp Glu Leu Glu Arg Leu Lys
        35                  40                  45

Glu Lys Arg Leu Gln Ala Leu Arg  Lys Ala Gln Gln Gln Lys Gln Glu
    50                  55                  60

Trp Leu Ser Lys Gly His Gly Glu  Tyr Arg Glu Ile Pro Ser Glu Arg
65                  70                  75                  80

Asp Phe Phe Gln Glu Val Lys Glu  Ser Glu Asn Val Val Cys His Phe
                85                  90                  95

Tyr Arg Asp Ser Thr Phe Arg Cys  Lys Ile Leu Asp Arg His Leu Ala
            100                 105                 110

Ile Leu Ser Lys Lys His Leu Glu  Thr Asn Phe Leu Lys Leu Asn Val
        115                 120                 125

Glu Lys Ala Pro Phe Leu Cys Glu  Arg Leu His Ile Lys Val Ile Pro
    130                 135                 140

Thr Leu Ala Leu Leu Lys Asp Gly  Lys Thr Gln Asp Tyr Val Val Gly
145                 150                 155                 160

Phe Thr Asp Leu Gly Asn Thr Asp Asp Phe Thr Thr Glu Thr Leu Glu
                165                 170                 175

Trp Arg Leu Gly Ser Ser Asp Ile Leu Asn Tyr Ser Gly Asn Leu Met
            180                 185                 190

Glu Pro Pro Phe Gln Asn Gln Lys Lys Phe Gly Thr Asn Phe Thr Lys
        195                 200                 205

Leu Glu Lys Lys Thr Met Arg Gly Lys Lys Tyr Asp Ser Asp Ser Asp
    210                 215                 220

Asp Asp
225
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<210> 5
<211> 4263
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(3705)

<400> 5

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ggg aat acc cag ctt cct ccc cgc aac ccg gtg aaa gcc aac gca atg   48
Gly Asn Thr Gln Leu Pro Pro Arg Asn Pro Val Lys Ala Asn Ala Met
  1               5                  10                  15

ttc ggt gcg ggg gac gag gac gac acc gat ttc ctc tcg ccg agc ggc   96
Phe Gly Ala Gly Asp Glu Asp Asp Thr Asp Phe Leu Ser Pro Ser Gly
             20                  25                  30

ggt gcc aga ttg gcc tca ctt ttt gga ctg gat cag gca gct gct ggc   144
Gly Ala Arg Leu Ala Ser Leu Phe Gly Leu Asp Gln Ala Ala Ala Gly
        35                  40                  45

cat gga aat gaa ttt ttc cag tac aca gcc cca aaa cag cct aag aaa   192
His Gly Asn Glu Phe Phe Gln Tyr Thr Ala Pro Lys Gln Pro Lys Lys
     50                  55                  60

ggc cag gga acg gca gca aca gga aat cag gca aca cca aaa aca gca   240
Gly Gln Gly Thr Ala Ala Thr Gly Asn Gln Ala Thr Pro Lys Thr Ala
 65                  70                  75                  80

cca gcc acc atg agc act ccc aca ata ctg gtc gca aca gca gtc cat   288
Pro Ala Thr Met Ser Thr Pro Thr Ile Leu Val Ala Thr Ala Val His
                 85                  90                  95

gca tat cga tac aca aat ggt caa tat gta aag cag ggc aaa ttt ggt   336
Ala Tyr Arg Tyr Thr Asn Gly Gln Tyr Val Lys Gln Gly Lys Phe Gly
            100                 105                 110

gct gca gtt ctg ggg aac cac aca gcc aga gag tat agg att ctt ctt   384
Ala Ala Val Leu Gly Asn His Thr Ala Arg Glu Tyr Arg Ile Leu Leu
        115                 120                 125

tat atc agt caa caa cag cca gtt acg gtt gct agg att cat gtg aac   432
Tyr Ile Ser Gln Gln Gln Pro Val Thr Val Ala Arg Ile His Val Asn
    130                 135                 140

ttt gag cta atg gtt cgg ccc aat aac tat agc acc ttt tat gat gac   480
Phe Glu Leu Met Val Arg Pro Asn Asn Tyr Ser Thr Phe Tyr Asp Asp
145                 150                 155                 160

cag aga cag aac tgg tcc atc atg ttt gag tcg gaa aag gct gct gtg   528
Gln Arg Gln Asn Trp Ser Ile Met Phe Glu Ser Glu Lys Ala Ala Val
                165                 170                 175
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gag ttc aat aag cag gtg tgc att gct aag tgc aac agt acc tct tcc   576
Glu Phe Asn Lys Gln Val Cys Ile Ala Lys Cys Asn Ser Thr Ser Ser
            180                 185                 190

ctg gat gca gtg ctc tcc cag gac ctc att gtg gca gac ggc cct gct   624
Leu Asp Ala Val Leu Ser Gln Asp Leu Ile Val Ala Asp Gly Pro Ala
        195                 200                 205

gta gaa gtt gga gat tct ttg gaa gtg gcc tat acc ggc tgg ctc ttt   672
Val Glu Val Gly Asp Ser Leu Glu Val Ala Tyr Thr Gly Trp Leu Phe
    210                 215                 220

cag aat cat gtg ctg ggc cag gtt ttc gac tcc act gct aac aaa gat   720
Gln Asn His Val Leu Gly Gln Val Phe Asp Ser Thr Ala Asn Lys Asp
225                 230                 235                 240

aag ttg ctt cgc ttg aag tta gga tca gga aaa gtc atc aag ggc tgg   768
Lys Leu Leu Arg Leu Lys Leu Gly Ser Gly Lys Val Ile Lys Gly Trp
                245                 250                 255

gag gat gga atg ctg ggc atg aaa aaa gga gga aag cga ttg ctt att   816
Glu Asp Gly Met Leu Gly Met Lys Lys Gly Gly Lys Arg Leu Leu Ile
            260                 265                 270

gtc cct cca gcc tgt gct gtt ggc tca gaa ggg gta ata ggc tgg act   864
Val Pro Pro Ala Cys Ala Val Gly Ser Glu Gly Val Ile Gly Trp Thr
        275                 280                 285

caa gca acg gac tcg atc ctg gtg ttc gag gtg gag gtt agg cgg gtg   912
Gln Ala Thr Asp Ser Ile Leu Val Phe Glu Val Glu Val Arg Arg Val
    290                 295                 300

aag ttt gcc aga gat tct ggc tct gat ggt cac agt gtt agt tcc cgc   960
Lys Phe Ala Arg Asp Ser Gly Ser Asp Gly His Ser Val Ser Ser Arg
305                 310                 315                 320

gat tct gca gct ccg tct ccc atc cct ggt gct gac aac ctc tct gct  1008
Asp Ser Ala Ala Pro Ser Pro Ile Pro Gly Ala Asp Asn Leu Ser Ala
                325                 330                 335

gat cct gtt gtg tca cca ccc aca tca ata cct ttc aaa tca ggg gag  1056
Asp Pro Val Val Ser Pro Pro Thr Ser Ile Pro Phe Lys Ser Gly Glu
            340                 345                 350

cca gct ctt cgt acc aaa tct aac tcc ctc agt gaa caa ctt gca ata  1104
Pro Ala Leu Arg Thr Lys Ser Asn Ser Leu Ser Glu Gln Leu Ala Ile
        355                 360                 365

aat aca agt ccc gat gca gtc aaa gcc aag ttg atc tct cgg atg gct  1152
Asn Thr Ser Pro Asp Ala Val Lys Ala Lys Leu Ile Ser Arg Met Ala
    370                 375                 380

aaa atg ggc cag ccc atg ctg ccc atc ctt cca cca cag ctg gat tcc  1200
Lys Met Gly Gln Pro Met Leu Pro Ile Leu Pro Pro Gln Leu Asp Ser
385                 390                 395                 400
```

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aat gat tca gaa atc gaa gat gtg aac act ctg caa gga ggt ggg cag   1248
Asn Asp Ser Glu Ile Glu Asp Val Asn Thr Leu Gln Gly Gly Gly Gln
            405                 410                 415

cct gtg gtg act ccg tcc gtc cag ccc tct ctt cag ccg gcc cat cca   1296
Pro Val Val Thr Pro Ser Val Gln Pro Ser Leu Gln Pro Ala His Pro
        420                 425                 430

gcg tta cca cag atg acc tca cag gca cct cag cca tct gtt act ggg   1344
Ala Leu Pro Gln Met Thr Ser Gln Ala Pro Gln Pro Ser Val Thr Gly
    435                 440                 445

ctc cag gca cct tct gct gcc tta atg caa gtg tca tct ctc gat tcc   1392
Leu Gln Ala Pro Ser Ala Ala Leu Met Gln Val Ser Ser Leu Asp Ser
450                 455                 460

cac tca gct gta tct gga aat gcc caa tcc ttt cag ccc tat gca ggt   1440
His Ser Ala Val Ser Gly Asn Ala Gln Ser Phe Gln Pro Tyr Ala Gly
465                 470                 475                 480

atg caa gcc tac gct tat ccc cag gca tct gcc gtc acc tcc cag ctg   1488
Met Gln Ala Tyr Ala Tyr Pro Gln Ala Ser Ala Val Thr Ser Gln Leu
            485                 490                 495

cag ccc gtt cgg cct ttg tac cca gca ccg ctc tct cag cct ccc cat   1536
Gln Pro Val Arg Pro Leu Tyr Pro Ala Pro Leu Ser Gln Pro Pro His
        500                 505                 510

ttc caa gga tca ggt gat atg gct tca ttt ctc atg act gaa gcc cgg   1584
Phe Gln Gly Ser Gly Asp Met Ala Ser Phe Leu Met Thr Glu Ala Arg
    515                 520                 525

caa cat aac act gaa att cga atg gca gtc agc aaa gtg gct gat aaa   1632
Gln His Asn Thr Glu Ile Arg Met Ala Val Ser Lys Val Ala Asp Lys
530                 535                 540

atg gat cat ctc atg act aag gtt gaa gag tta cag aaa cat agt gct   1680
Met Asp His Leu Met Thr Lys Val Glu Glu Leu Gln Lys His Ser Ala
545                 550                 555                 560

ggc aat tcc atg ctt att cct agc atg tca gtt aca atg gaa aca agc   1728
Gly Asn Ser Met Leu Ile Pro Ser Met Ser Val Thr Met Glu Thr Ser
            565                 570                 575

atg att atg agc aac atc cag cga atc att cag gaa aat gaa aga ttg   1776
Met Ile Met Ser Asn Ile Gln Arg Ile Ile Gln Glu Asn Glu Arg Leu
        580                 585                 590

aag caa gag atc ctt gaa aag agc aat cgg ata gaa gaa cag aat gac   1824
Lys Gln Glu Ile Leu Glu Lys Ser Asn Arg Ile Glu Glu Gln Asn Asp
    595                 600                 605

aag att agt gaa cta att gaa cga aat cag agg tat gtt gag cag agt   1872
Lys Ile Ser Glu Leu Ile Glu Arg Asn Gln Arg Tyr Val Glu Gln Ser
610                 615                 620
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aac ctg atg atg gag aag agg aac aac tca ctt cag aca gcc aca gaa   1920
Asn Leu Met Met Glu Lys Arg Asn Asn Ser Leu Gln Thr Ala Thr Glu
625                 630                 635                 640

aac aca cag gca aga gta ttg cat gct gaa caa gag aag gcc aag gtg   1968
Asn Thr Gln Ala Arg Val Leu His Ala Glu Gln Glu Lys Ala Lys Val
                645                 650                 655

aca gag gag tta gca gcg gcc act gcg cag gtc tct cat ctg cag ctg   2016
Thr Glu Glu Leu Ala Ala Ala Thr Ala Gln Val Ser His Leu Gln Leu
            660                 665                 670

aaa atg act gct cac caa aaa aag gaa aca gag ctg cag atg cag ctg   2064
Lys Met Thr Ala His Gln Lys Lys Glu Thr Glu Leu Gln Met Gln Leu
        675                 680                 685

aca gaa agc ctg aag gag aca gat ctt ctc agg ggc cag ctc acc aaa   2112
Thr Glu Ser Leu Lys Glu Thr Asp Leu Leu Arg Gly Gln Leu Thr Lys
    690                 695                 700

gtg cag gca aag ctc tca gag ctc caa gaa acc tct gag caa gca cag   2160
Val Gln Ala Lys Leu Ser Glu Leu Gln Glu Thr Ser Glu Gln Ala Gln
705                 710                 715                 720

tcc aaa ttc aaa agt gaa aag cag aac cgg aaa caa ctg gaa ctc aag   2208
Ser Lys Phe Lys Ser Glu Lys Gln Asn Arg Lys Gln Leu Glu Leu Lys
                725                 730                 735

gtg aca tcc ctg gag gag gaa ctg act gac ctt cga gtt gag aag gag   2256
Val Thr Ser Leu Glu Glu Glu Leu Thr Asp Leu Arg Val Glu Lys Glu
            740                 745                 750

tcc ttg gaa aag aac ctc tca gaa agg aaa aag aag tca gct caa gag   2304
Ser Leu Glu Lys Asn Leu Ser Glu Arg Lys Lys Lys Ser Ala Gln Glu
        755                 760                 765

cgt tct cag gcc gag gag gag ata gat gaa att cgc aag tca tac cag   2352
Arg Ser Gln Ala Glu Glu Glu Ile Asp Glu Ile Arg Lys Ser Tyr Gln
    770                 775                 780

gag gaa ttg gac aaa ctt cga cag ctc ttg aaa aag act cga gtg tcc   2400
Glu Glu Leu Asp Lys Leu Arg Gln Leu Leu Lys Lys Thr Arg Val Ser
785                 790                 795                 800

aca gac caa gca gct gca gag cag ctg tct tta gta cag gct gag cta   2448
Thr Asp Gln Ala Ala Ala Glu Gln Leu Ser Leu Val Gln Ala Glu Leu
                805                 810                 815

cag acc cag tgg gaa gca aaa tgt gaa cat ttg ttg gcc tcc gcc aag   2496
Gln Thr Gln Trp Glu Ala Lys Cys Glu His Leu Leu Ala Ser Ala Lys
            820                 825                 830

gat gag cac ctg cag cag tac cag gag gtg tgc gca cag aga gat gcc   2544
Asp Glu His Leu Gln Gln Tyr Gln Glu Val Cys Ala Gln Arg Asp Ala
        835                 840                 845
```

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tac cag cag aag ctg gta caa ctt cag gaa aag tgt tta gcc ctc cag   2592
Tyr Gln Gln Lys Leu Val Gln Leu Gln Glu Lys Cys Leu Ala Leu Gln
    850                 855                 860

gcc caa atc aca gct ctc acc aag caa aat gaa cag cac atc aag gaa   2640
Ala Gln Ile Thr Ala Leu Thr Lys Gln Asn Glu Gln His Ile Lys Glu
865                 870                 875                 880

cta gag aag aac aag tcc cag atg tct ggg gtt gaa gct gct gca tct   2688
Leu Glu Lys Asn Lys Ser Gln Met Ser Gly Val Glu Ala Ala Ala Ser
            885                 890                 895

gac ccc tca gag aag gtc aag aag atc atg aac cag gtg ttc cag tcc   2736
Asp Pro Ser Glu Lys Val Lys Lys Ile Met Asn Gln Val Phe Gln Ser
        900                 905                 910

tta cgg aga gag ttt gag ctg gag gaa tct tac aat ggc agg acc att   2784
Leu Arg Arg Glu Phe Glu Leu Glu Glu Ser Tyr Asn Gly Arg Thr Ile
    915                 920                 925

ctg gga acc atc atg aat acg atc aag atg gtg act ctt cag ctg tta   2832
Leu Gly Thr Ile Met Asn Thr Ile Lys Met Val Thr Leu Gln Leu Leu
930                 935                 940

aac caa cag gag caa gag aag gaa gag agc agc agt gaa gaa gaa gaa   2880
Asn Gln Gln Glu Gln Glu Lys Glu Glu Ser Ser Ser Glu Glu Glu Glu
945                 950                 955                 960

gaa aaa gca gaa gag cgg cca cga aga cct tcc cag gag cag tca gcc   2928
Glu Lys Ala Glu Glu Arg Pro Arg Arg Pro Ser Gln Glu Gln Ser Ala
            965                 970                 975

tca gcc agt tct ggg cag cct caa gca ccc ctg aat agg gag agg cca   2976
Ser Ala Ser Ser Gly Gln Pro Gln Ala Pro Leu Asn Arg Glu Arg Pro
        980                 985                 990

gag tcc ccc atg gtg ccc tca gag cag gtg gtc gag gaa gct gtc ccg   3024
Glu Ser Pro Met Val Pro Ser Glu Gln Val Val Glu Glu Ala Val Pro
    995                 1000                1005

ttg cct cct cag gcc ctc acc act tcc cag gat gga cac aga agg aaa   3072
Leu Pro Pro Gln Ala Leu Thr Thr Ser Gln Asp Gly His Arg Arg Lys
1010                1015                1020

ggg gac tca gaa gct gag gca ctc tca gag ata aaa gat ggt tcc ctt   3120
Gly Asp Ser Glu Ala Glu Ala Leu Ser Glu Ile Lys Asp Gly Ser Leu
1025                1030                1035                1040

cca ccc gaa ctg tct tgc atc cca tcc cac aga gtt cta ggg ccc ccg   3168
Pro Pro Glu Leu Ser Cys Ile Pro Ser His Arg Val Leu Gly Pro Pro
            1045                1050                1055

act tca att cca cct gag ccc cta ggc cct gta tcc atg gac tct gag   3216
Thr Ser Ile Pro Pro Glu Pro Leu Gly Pro Val Ser Met Asp Ser Glu
        1060                1065                1070
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tgt gag gag tca ctt gct gcc agc cca atg gca gct aag ccc gac aac   3264
Cys Glu Glu Ser Leu Ala Ala Ser Pro Met Ala Ala Lys Pro Asp Asn
      1075                1080                1085

cca tca gga aag gtc tgt gtc agg gaa gta gca cca gat ggc cca cta   3312
Pro Ser Gly Lys Val Cys Val Arg Glu Val Ala Pro Asp Gly Pro Leu
   1090                1095                1100

caa gaa agc tcc aca aga ctg tcc ctg act tca gac ccc gag gag ggg   3360
1105                1110                1115                1120

gac cca ctg gcc tta ggg cct gaa agc cca gga gag cct cag cct cca   3408
Asp Pro Leu Ala Leu Gly Pro Glu Ser Pro Gly Glu Pro Gln Pro Pro
               1125                1130                1135

cag ctc aag aaa gat gat gtc act agc tcc acc ggt ccc cac aag gag   3456
Gln Leu Lys Lys Asp Asp Val Thr Ser Ser Thr Gly Pro His Lys Glu
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ctg tca agc aca gag gca ggt tcc aca gtt gca gga gca gcc ctc aga   3504
Leu Ser Ser Thr Glu Ala Gly Ser Thr Val Ala Gly Ala Ala Leu Arg
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Pro Ser His His Ser Gln Arg Ser Ser Leu Ser Gly Asp Glu Glu Asp
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cct gag gag gag gat gaa gac gag gtg agc atg aag gga cgc ccg ccc   3648
Pro Glu Glu Glu Asp Glu Asp Glu Val Ser Met Lys Gly Arg Pro Pro
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ctg gga tga agacccagga aactggtgca aaggtttctc tgcaaccctt          3745
Leu Gly
      1235

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His Gly Asn Glu Phe Phe Gln Tyr Thr Ala Pro Lys Gln Pro Lys Lys
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Gly Gln Gly Thr Ala Ala Thr Gly Asn Gln Ala Thr Pro Lys Thr Ala
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Ala Tyr Arg Tyr Thr Asn Gly Gln Tyr Val Lys Gln Gly Lys Phe Gly
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Ala Ala Val Leu Gly Asn His Thr Ala Arg Glu Tyr Arg Ile Leu Leu
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Phe Glu Leu Met Val Arg Pro Asn Asn Tyr Ser Thr Phe Tyr Asp Asp
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Gln Asn His Val Leu Gly Gln Val Phe Asp Ser Thr Ala Asn Lys Asp
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Asp Ser Ala Ala Pro Ser Pro Ile Pro Gly Ala Asp Asn Leu Ser Ala
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Asp Pro Val Val Ser Pro Pro Thr Ser Ile Pro Phe Lys Ser Gly Glu
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Pro Ala Leu Arg Thr Lys Ser Asn Ser Leu Ser Glu Gln Leu Ala Ile
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Asn Thr Ser Pro Asp Ala Val Lys Ala Lys Leu Ile Ser Arg Met Ala
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385                 390                 395                 400

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Ala Leu Pro Gln Met Thr Ser Gln Ala Pro Gln Pro Ser Val Thr Gly
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Gln Pro Val Arg Pro Leu Tyr Pro Ala Pro Leu Ser Gln Pro Pro His
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Gln His Asn Thr Glu Ile Arg Met Ala Val Ser Lys Val Ala Asp Lys
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Asn Leu Met Met Glu Lys Arg Asn Asn Ser Leu Gln Thr Ala Thr Glu
625                 630                 635                 640

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Asp Pro Ser Glu Lys Val Lys Lys Ile Met Asn Gln Val Phe Gln Ser
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Leu Gly Thr Ile Met Asn Thr Ile Lys Met Val Thr Leu Gln Leu Leu
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965 970 975

Ser Ala Ser Ser Gly Gln Pro Gln Ala Pro Leu Asn Arg Glu Arg Pro
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Lys Ala Thr Pro Asp Ser Leu Glu Pro Ala Gly Pro Ser Ser Pro Ala
35 40 45

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Ser Val Thr Val Thr Val Gly Asp Glu Gly Ala Asp Thr Pro Val Gly
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gct aca cca ctc att ggg gat gaa tct gag aat ctt gag gga gat ggg 240
Ala Thr Pro Leu Ile Gly Asp Glu Ser Glu Asn Leu Glu Gly Asp Gly
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tct gaa ccc cct cca gcc acc acg agc cca gag gga cag ccc aag gtc   480
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aag acc cca tct cta aaa gaa gtt taa aagaatgttt caaaggccag         575
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            180                 185

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Ala Thr Pro Leu Ile Gly Asp Glu Ser Glu Asn Leu Glu Gly Asp Gly
65                  70                  75                  80

Asp Leu Arg Gly Gly Arg Ile Leu Leu Gly His Ala Thr Lys Ser Phe
                85                  90                  95

Pro Ser Ser Pro Ser Lys Gly Gly Ser Cys Pro Ser Arg Ala Lys Met
            100                 105                 110

Ser Met Thr Gly Ala Gly Lys Ser Pro Pro Ser Val Gln Ser Leu Ala
        115                 120                 125
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Met Arg Leu Leu Ser Met Pro Gly Ala Gln Gly Ala Ala Ala Ala Gly
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Ser Glu Pro Pro Pro Ala Thr Thr Ser Pro Glu Gly Gln Pro Lys Val
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His Arg Ala Arg Lys Thr Met Ser Lys Pro Gly Asn Gly Gln His Thr
                165                 170                 175

Lys Thr Pro Ser Leu Lys Glu Val
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WO 01/58937 A3

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(21) International Application Number: PCT/GB01/00541

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0002981.9	9 February 2000 (09.02.2000)	GB

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(74) Agent: **IRVINE, Claire, Jonquil**; J.A. Kemp & Co., 14 South Square, Gray's Inn, London WC1R 5LX (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

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11 April 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/58937 A3

(54) Title: INTERFERON-ALPHA INDUCED GENES

(57) Abstract: The present disclosure relates to identification of genes upregulated by interferon-α administration, in particular the human genes corresponding to the cDNA sequences in GenBank designated g4586459, g2342476, g3327161 and g4529886. Determination of expression products of these genes is proposed as having utility in predicting responsiveness to treatment with interferon-α and other interferons which act at the Type 1 interferon receptor. Therapeutic use of the proteins encoded by the same genes is also envisaged.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 01/00541

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/12 C07K14/47 C07K16/18 A61K38/17 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EMBL, EPO-Internal, BIOSIS, WPI Data, CHEM ABS Data, MEDLINE, EMBASE, LIFESCIENCE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE EMBL 'Online! Accession Nr.: AB025254, 1 April 1999 (1999-04-01) HIROSE T: "CDC2 related kinase, PCTAIRE 2 binding protein that contains tudor domain." XP002168215 see sequence abstract --- -/--	1-5

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 August 2001	03.09.01

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Bassias, I

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE EMBL 'Online! Accession Nr.: AB006679, 23 August 1997 (1997-08-23) SHIOSAKA T: "Differential expression of 1-4 gene in functionally distinct ME-1 subclones" XP002174639 see sequence abstract ---	1-5
X	DATABASE EMBL 'Online! Accession Nr.: AF027733, 8 November 1997 (1997-11-08) BRULE S AND LUSSIER JG: "Bovine ATP binding protein" XP002174640 see sequence abstract ---	1-5
X	DATABASE EMBL 'Online! Accession Nr.: AB014574, 6 February 1999 (1999-02-06) OHARA O ET AL.: "direct submission" XP002174641 see sequence abstract ---	1-5
X	DATABASE EMBL 'Online! Accession Nr.: AF134726, 27 March 1999 (1999-03-27) ROWEN L ET AL. : "Sequence of the human major histocompatibility complex class III region" XP002174642 see sequence "GI:4529888" abstract ---	1-5
X	DATABASE EMBL 'Online! Accession Nr.: AF109906, 10 December 1998 (1998-12-10) ROWEN L ET AL.: "Sequence of the mouse MHC class III region" XP002174643 see sequence "GI3986769" abstract ---	1-5
X	DATABASE EMBL 'Online! AI828004, 13 July 1999 (1999-07-13) XP002174644 see sequence abstract --- -/--	2-5

INTERNATIONAL SEARCH REPORT

Intern ial Application No
PCT/GB 01/00541

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE EMBL 'Online! AA934369, 29 April 1998 (1998-04-29) XP002174645 see sequence abstract	2-5
Y	EP 0 242 329 A (CIBA GEIGY AG) 21 October 1987 (1987-10-21) the whole document, in particular: page 2, first paragraph; page 3, third paragraph; page 4, paragraphs 1-3	1-14
Y	HORISBERGER M A ET AL: "IFN-ALPHA INDUCED HUMAN 78 KD PROTEIN: PURIFICATION AND HOMOLOGIES WITH THE MOUSE MX PROTEIN, PRODUCTION OF MONOCLONAL ANTIBODIES, ANDPOTENTIATION EFFECT OF IFN-GAMMA" JOURNAL OF INTERFERON RESEARCH,US,MARY ANN LIEBERT, INC., NEW YORK, NY, vol. 7, 1 August 1987 (1987-08-01), pages 331-343, XP002059946 ISSN: 0197-8357 the whole document	1-14
Y	US 5 834 235 A (RICH STEVEN A ET AL) 10 November 1998 (1998-11-10) the whole document, in particular column 1, lines 55-67 and column 2, line 59 - column 3, line 39	1-14

6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 01/00541

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 8-12
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 8-12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Claims Nos.: 8-12

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: Claims 1-14 (all partially)

Isolated polypeptide comprising SEQ ID NO: 2, variants and fragments thereof, the corresponding polynucleotide (SEQ ID NO: 1), pharmaceutical compositions comprising said polypeptide or polynucleotide, antibodies and antisense sequences against said molecules and the use of said molecules for preparation of medicaments, for therapy and for prediction of responsiveness of a patient to treatment with a Type I interferon.

2. Claims: Claims 1-14 (all partially)

Isolated polypeptide comprising SEQ ID NO: 4, variants and fragments thereof, the corresponding polynucleotide (SEQ ID NO: 3), pharmaceutical compositions comprising said polypeptide or polynucleotide, antibodies and antisense sequences against said molecules and the use of said molecules for preparation of medicaments, for therapy and for prediction of responsiveness of a patient to treatment with a Type I interferon.

3. Claims: Claims 1-14 (all partially)

Isolated polypeptide comprising SEQ ID NO: 6, variants and fragments thereof, the corresponding polynucleotide (SEQ ID NO: 5), pharmaceutical compositions comprising said polypeptide or polynucleotide, antibodies and antisense sequences against said molecules and the use of said molecules for preparation of medicaments, for therapy and for prediction of responsiveness of a patient to treatment with a Type I interferon.

4. Claims: Claims 1-14 (all partially)

Isolated polypeptide comprising SEQ ID NO: 8, variants and fragments thereof, the corresponding polynucleotide (SEQ ID NO: 7), pharmaceutical compositions comprising said polypeptide or polynucleotide, antibodies and antisense sequences against said molecules and the use of said molecules for preparation of medicaments, for therapy and for prediction of responsiveness of a patient to treatment with a Type I interferon.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern al Application No
PCT/GB 01/00541

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0242329 A	21-10-1987	AT 125304 T	15-08-1995
		AU 608216 B	28-03-1991
		AU 7151087 A	22-10-1987
		CA 1340289 A	29-12-1998
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		DE 3751409 T	25-01-1996
		DK 193187 A	16-10-1987
		ES 2074420 T	16-09-1995
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		JP 2107176 C	06-11-1996
		JP 8022880 B	06-03-1996
		JP 62270599 A	24-11-1987
		PT 84670 A,B	01-05-1987
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		US 5739290 A	14-04-1998
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